

## Pertussis vaccine: Is the controversy nearly over?

Brian Goldman, MD

*This is proving to be a pivotal year in the history of pertussis vaccine, one of medicine's polarizing issues. Proponents say the vaccine may have some annoying side effects, but is basically safe. They've been heartened by a landmark British ruling that concluded the vaccine is highly unlikely to cause encephalopathy. Opponents — mostly parents of children allegedly injured by it — say it is dangerous and should not be used. In a judgement ex-*

*pected this fall, a judge of the Ontario Supreme Court will announce on which side of the fence Canadian courts sit. [Ed. note: As this issue of CMAJ went to press the judge dismissed that lawsuit, brought by Donna and Colin Rothwell.] Meanwhile, an international quest for a safer pertussis vaccine goes on. In a series of articles, CMAJ contributing editor Dr. Brian Goldman will take a close look at this controversial subject.*

**H**e'll never know it, but June 9th, 1988, was a very special day for Patrick Rothwell. Patrick is 9 and lives in Burlington, Ont., with his parents, Donna and Colin Rothwell. For them, 1988 will always be the year their son got his day in court.

*Brian Goldman, a Toronto emergency physician, is a CMAJ contributing editor.*

The Rothwells claim Patrick was a happy, healthy baby until June 26, 1979, the day he received the third of three primary immunizations with DPTP (diphtheria-pertussis-tetanus-polio) vaccine. The first and second immunizations were apparently administered without incident, on April 20 and May 25, respectively. Following the third one, though, his parents say Patrick developed a prolonged high-pitched cry and became jittery. In

the weeks that followed, he began missing developmental milestones. When he was 9 months old, doctors discovered he was blind.

The Rothwells responded by launching a \$15-million lawsuit against two Burlington family physicians, Drs. Daniel Raes and Sheila Hall, as well as the manufacturer of the vaccine, Connaught Laboratories, and the Ontario Ministry of Health. They allege that the defendants did not warn them pertussis vaccine might cause brain damage.

The case is being heard by the Supreme Court of Ontario, and by odd coincidence the judge is Mr. Justice John Osler, a grandnephew of Sir William Osler. "Patrick Rothwell has suffered substantially as a result of this vaccine", William Dunlop, lawyer for the Rothwells, said in his closing arguments. "He is blind, he is unable to sit up without assistance. He can't walk, he can't talk, he can't toilet himself. He will be dependent on his parents for the rest of his life."

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**lawyer William Dunlop**

Defence lawyers counter that Patrick, whose monozygotic twin died between 33 and 35 weeks' gestation, was not neurologically normal at birth. They argue that the boy's unfolding neurologic problems were inevitable, and had nothing to do with his immunization.

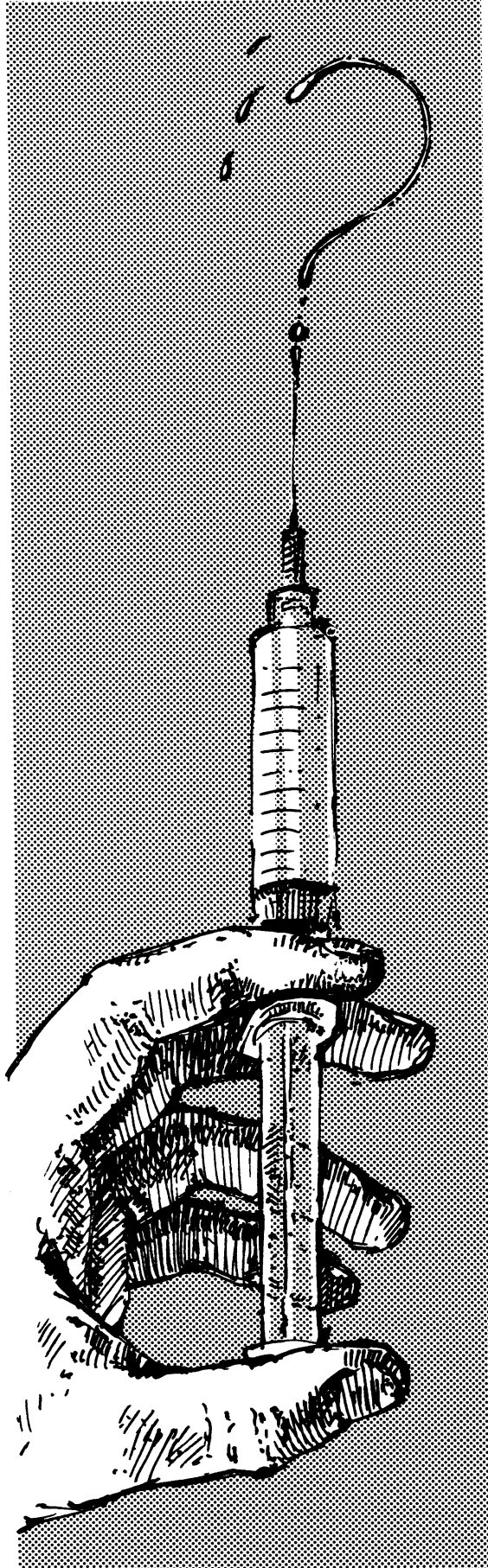
The case epitomizes the 40-year battle that has been waged since the first case reports of toxicity related to pertussis vaccine were published. It is a battle of minds between those who believe the vaccine can have tragic neurologic consequences and those who say it does not. On the former side are the parents of a few hundred children with stories similar to Patrick's, plus a small number of doctors who sympathize with them. On the latter are eminent physicians and bodies such as the Canadian Paediatric Society and the Centers for Disease Control in Atlanta. In some cases, governments have responded to the concerns of parents; at different times, both Sweden and Great Britain have suspended the distribution of the vaccine.

The Rothwell verdict is expected late in 1988, and the stakes are enormous. Experts say that between 5 and 15 lawsuits by other Canadian parents will be launched if the Rothwells win.

Nancy Howes, spokesperson for an organization called the Association for Vaccine Damaged Children, believes passionately that her 4-year-old daughter Patricia was damaged by pertussis vaccine. She told me that the newest member of the 153-couple organization joined just 2 hours before our interview. Like the other parents in the group, she is angry and frustrated with the medical profession and distraught about her child.

"I'm past the point of crying", she says. "Somebody has to pay for the damage that has been done to my daughter. The Rothwell case has been the one to go first. Every other case waiting to go is just in limbo."

She hopes Canadian jurists will follow the American example. Parents in the United States



have banded together under an organization called "Dissatisfied Parents Together", better known by its abbreviation, DPT. Its members have filed numerous lawsuits against physicians and vaccine manufacturers, and have been awarded as much as \$15 million (US). The huge awards have played havoc with vaccine manufacturers and both Wyeth Laboratories, Inc., and Parke-Davis have pulled out of the vaccine business. Connaught Laboratories and Lederle Laboratories stayed in operation, but prices skyrocketed to cover the cost of litigation and self-insurance.

Two triumphs have made 1988 a banner year for Dissatisfied Parents Together. On Oct. 1st, the National Childhood Vaccine Injury Act went into effect, providing \$80 million (US) per year in no-fault benefits to injured children, a result of intense lobbying by the parents. The second victory involved a Wichita, Kansas, jury that found Wyeth Laboratories negligent in the design and testing of its pertussis vaccine. More important, the case set a national precedent — the jury decided that the vaccine causes brain damage.

Canadian lawyers insist that American decisions seldom have much impact on Canadian courts. As well, the Rothwell case is being decided by a judge, not a jury. Juries, they argue, respond more to the emotional pleas of plaintiffs than to the strict rules concerning findings of negligence.

Still, things have not always looked bright for Canadian proponents of pertussis vaccine. Early last spring, however, they got a break when a British court decided against a British family. The Right Honourable Lord Justice Stuart-Smith ruled that lawyers for Susan Loveday, a 17-year-old girl with severe brain damage, failed to prove negligence. More importantly, he ruled that lawyers acting for Loveday failed to prove that pertussis vaccine can cause permanent brain damage in young children.

In Canada, Dr. Garry Humphreys, the medical director at Connaught Laboratories, was cautiously optimistic about the Loveday verdict. "We are of the belief that the vaccine does not cause brain damage", he says. "Yes, we're quite pleased with the decision. We think it was a very erudite one."

At the heart of the Loveday

the risk of brain damage or death from the vaccine was 1 in 310 000, a figure that became a benchmark around the world.

When the seven cases were re-examined, however, three of the children first reported to be dead or neurologically impaired turned out to be alive and well. Once those cases were subtracted, the results lost their statistical

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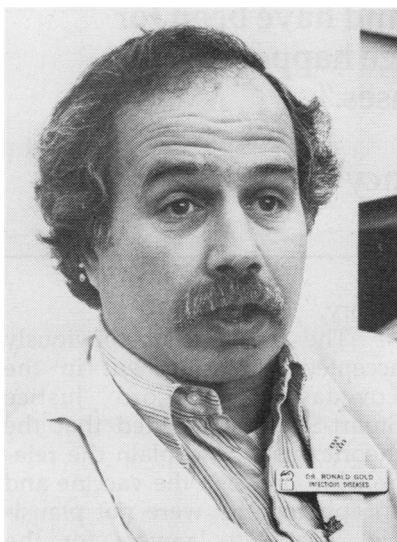
verdict was a reanalysis of scientific data collected in a British study. That survey, known as the National Childhood Encephalopathy Study (NCES), reported on all children between 2 and 35 months of age who were admitted to hospital with serious neurologic conditions. The study was financed by the British government in response to a rash of highly publicized cases of suspected pertussis toxicity. Seven infants in the study group were found to have had a pertussis vaccination within 7 days of admission. In a report published in 1981, the authors calculated that

significance. Humphreys says that premature conclusions arising from the study created a "myth" regarding the toxicity of the vaccine. "One of the challenges of any organization is to disprove certain myths created with regard to a product", he says. "It's sometimes very, very difficult to combat the myth that arises."

Connaught Laboratories is the second largest supplier of biological products to western nations. It is the main supplier of DPT vaccine in Canada and one of only two manufacturers supplying it in the United States. In addition, Connaught supplies vaccine to many developing nations. Humphreys refuses to speculate on the implications of the Loveday decision with respect to the Rothwell case, but promises that Connaught will "probably have a few words to say following that decision".

It should be pointed out that vaccines used in different countries vary in content and strength. The vaccine produced by Connaught for use in Canada, for instance, is not identical to that manufactured by its American subsidiary.

Dr. Ronald Gold, head of the Division of Infectious Diseases at Toronto's Hospital for Sick Children, summarized the Loveday



**Gold: hard to prove negative**

decision at a conference sponsored by the Ontario Medical Association last June. In an interview following that address, Gold told *CMAJ* he is satisfied with the conclusions reached in the Loveday case, but he does not believe it eliminates all concerns.

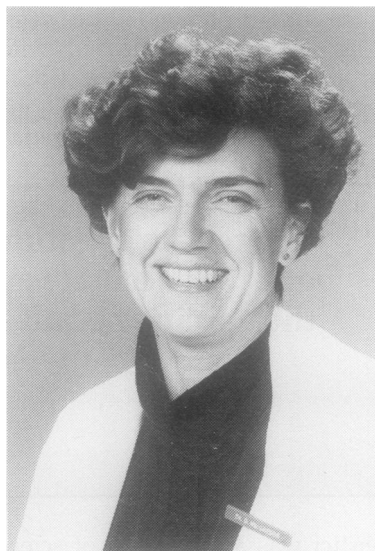
"No issue is ever put to rest scientifically", he says. "As the judge points out, no one is ever going to prove that pertussis vaccine or any other vaccine can never do something, because it's very difficult to prove the negative."

Gold's conclusion? "If it [damage] occurs at all, it's extremely rare. And it's certainly so rare that there's no question in my mind it's much better to vaccinate every child than to avoid the vaccine because of fear of harm to the child."

Gold says the NCES authors shouldn't shoulder all the blame for reaching premature conclusions about pertussis vaccine. "It was very unfortunate, in that there was a lot of pressure put on the researchers by the British government to publish prematurely", he charges.

He's hoping they won't make the same mistake again. The NCES was the subject of intense peer review during the 5th International Symposium on Pertussis, held recently in Copen-

signs and symptoms seemed to emerge: fever, vomiting, "jitteriness", inconsolable crying, seizures, and collapse or shocklike state. They usually appeared 24



MacGregor: still a theory

to 48 hours after vaccination.

Describing a syndrome is easy, but proving its existence is another matter, says Dr. Daune MacGregor, a pediatric neurologist at the Hospital for Sick Children. "Sure, I'd love to have neurophysiological or pathological evidence of it [toxicity due to pertussis vaccine]", she says. "In the absence of evidence, the relationship between pertussis vaccine and encephalopathy is still a

— to prove on epidemiologic grounds that encephalopathy caused by the vaccine exists.

Dr. John Frank, an epidemiologist at the University of Toronto, was asked by lawyers for Connaught Laboratories to interpret court transcripts from the Loveday case. For months he pored over transcripts piled more than half a metre high in his office. More than 1 year ago, Frank predicted that the British court would dismiss the case. It's not surprising that Lord Justice Stuart-Smith did just that — he has a university degree in epidemiology.

Frank says that the NCES is the definitive study of pertussis-related toxicity: "That study will not be repeated anywhere for some time." He notes that researchers from the Centers for Disease Control are in the midst of a major study of their own. "The Americans think they can do it, but they don't have the reporting system that they do in Great Britain under the National Health Service."

Frank adds that the British study cast doubt on a second widely held belief about pertussis vaccine, that it somehow worsens pre-existing neurologic disease. "Some children with neurological deficits that predate the vaccine have the deficit unmasked by the vaccine, or the febrile illness arising from the vaccine", he says. "What the clinician sees is the unmasking of a deficit already there, but quiescent. There isn't any evidence at all that children are made abnormal or that abnormal children are made more abnormal by the vaccine."

A large part of the scientific war is being waged through controlled studies, but part of it is being fought in the political arena. Nancy Howes appeared before an Ontario legislature committee that was holding hearings on Bill 52, legislation compelling physicians to inform parents of possible adverse effects before a vaccination is administered.

For Howes, it was an opportunity to meet experts such as Gold on an even footing. "You know, the man endorses the [im-

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**Nancy Howes**

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hagen. Organizers of a meeting cosponsored by the Centers for Disease Control and the American Academy of Pediatrics hope to do the same.

The first case reports of encephalopathy related to pertussis immunizations were published in the late 1940s. As the number of reports mounted, a pattern of

theory."

The British court obviously accepted that argument in the Loveday case. Lord Justice Stuart-Smith concluded that the theories used to explain the relationship between the vaccine and encephalopathy were not plausible. That left lawyers for the Loveday family with one option

munization] program to the nines", she charges. "All you doctors are aware — and have been aware for years — that it [brain damage] happens, albeit in rare cases. That's where the real anger is, because doctors just aren't willing to come out and admit it.

"[You] just deny it so terribly. [You] say that children are more apt to develop seizure disorders between 2 and 6 months of age. [You] say that if [you] vaccinated our child during that time and the child developed a seizure disorder, then it's just coincidence. Now come on. Give me a break."

Gold has a different recollection of the hearings. "I was described by one of the parents as [someone] who is going around killing children in Ontario. They obviously regard me with a great deal of antipathy [because of my] speaking against them, attacking their position.

"I find it very disheartening talking with many of them, because it's like talking to any believer — you can't argue with them.

"People are very dissatisfied with the unknown and [with] not having an answer [or] something to blame. I don't think there's any way of persuading someone who has had this happen to their child that there was a prenatal brain injury or a perinatal brain injury that we haven't been able to diagnose.

"I sympathize with them. I certainly support a compensation law. I have no trouble with the parents and I don't feel antipathy towards parents who get angry with me."

But there he draws the line, saying he has difficulty trying to understand "people like Dr. Kevin Geraghty, because he refuses to look facts in the face".

Geraghty, a pediatric immunologist from Pinole, California, has earned a reputation as one of the harshest critics of pertussis vaccine. He spent 4 days on the stand as an expert witness for the plaintiffs in the Rothwell case.

He says he became interested in vaccine-related toxicity

when he read of several case reports concerning unexplained infant deaths following administration of DPT vaccine. As an expert witness in several lawsuits, he was able to read correspondence and other relevant documents produced by the vac-

Geraghty has not produced a body of significant research; a literature search revealed that he has had two letters published in pediatric journals, plus an abstract of a small study showing an association between histocompatibility leukocyte antigen B18

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cine manufacturers.

He is convinced that pertussis vaccine causes encephalopathy — court transcripts show this was his position in the Rothwell case. Further, he charges that Connaught has long been aware that the vaccine causes toxicity.

"Connaught Laboratories Limited had abundant documentation showing that there were technical problems with [its] vaccine that were amenable to research", Geraghty argues. He says Connaught was on the cutting edge of research into safer vaccines years ago, but at the time chose not to pursue that research, for reasons he declined to reveal.

"There were abundant internal documents showing that Connaught was aware of the problem . . .", he charges. "That data failed to trickle down to the average practitioner, and I view myself as being a self-appointed spokesperson for that innocent clinician, who one day wakes up and loses this game of vaccine roulette."

Gold says most of Geraghty's charges are unsubstantiated. "He's on a hobbyhorse that's gotten him a lot of publicity that he would never otherwise have gotten for any reason", Gold argues. "He makes some very wild accusations about people that are impossible to justify."

and the tendency of children to react to pertussis vaccine within 24 hours of its administration. The abstract appeared in the *Annals of Allergy* in 1985. He submitted a full article based on the study to the *Journal of the American Medical Association*, but says he balked at the editor's suggestions about revising it.

When asked, Geraghty refused to produce comments that substantiate his position regarding Connaught.

Dr. Alan West, one of the lawyers representing Connaught, refused to comment on Geraghty's charges. However, he says the credibility of all witnesses at the trial — Geraghty included — is at issue.

At the same time, Connaught and other vaccine manufacturers are spending time and money in an effort to develop new and safer pertussis vaccines. Purged of endotoxins, these acellular vaccines are believed to be safer than whole-cell ones. Gold says that research into them is justified.

"There's no question that the acellular vaccine causes very few of the common reactions, the fever, the irritability and the pain", he says.

The big question in the minds of parents and physicians alike is whether or not acellular pertussis vaccine prevents other far more serious problems. ■